

Given, however, a strain of the knee, a more prominent and tender tubercle on the injured side and an x-ray taken in the same plane as the skiagraph of the normal knee, and showing a wider separation of the epiphysis, or an avulsion of a small portion, we may be reasonably sure of the diagnosis.

(3) *Treatment*.—The bursa directly above the tubercle and beneath the patella tendon in a small percentage of cases communicates directly with the joint. There may be enough bursitis set up to bring about a definite synovitis, for which complete immobilization may be necessary. Ordinarily treatment directed toward lessening the pull of the patella tendon and restricting motion is adequate for the relief of the symptoms. A tightly applied crisscross strapping of adhesive plaster extending around about two thirds of the circumference of the leg, and applied from perhaps one inch below the tubercle to one inch above the lower border of the patella, has proved a satisfactory method of accomplishing this end. This is renewed as it becomes loosened, perhaps every ten days, for about a month, and a flannel bandage worn for a few weeks after this.

(4) *Prognosis*.—The prognosis with treatment has been uniformly good as to relief of pain and restoration of function. A case in which the end result is shown in Fig. 11 had been treated unintelligently, because of failure to make the diagnosis, and the history has been one of considerable pain and annoyance, coupled with restricted exercise for a period of years.

(6) CONCLUSIONS.

The adolescent tibial tubercle, from its situation and mode of development, is susceptible to injuries, especially in athletic subjects. These lesions are usually caused by a violent contraction of the quadriceps extensor.

Fracture and complete avulsions of the tubercle are rare, cause loss of function, and are easily diagnosed, usually clinically and always by means of the x-ray.

Avulsions of a small portion and partial separation of the tubercle are more common. They do not cause complete loss of function, but without treatment, long continued serious annoyance. The diagnosis should be made by a combination of the clinical and x-ray pictures, and before the latter are accepted as evidence both knees should be skiagraphed and accurate technique observed.

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THE SIDE CHAIN THEORY.¹

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RECENT studies of immunity are so interesting and so full of promise of helpfulness, and yet withal so hard to get hold of, that we who are far from being masters in pathology find plenty of reason for trying to make them clear to each other.

Organotherapy was at least easy to understand. Through the work of Horsley, Murray and others, the homely, old counsel, "Eat a part to strengthen a part" becomes, to a limited extent, a therapeutic principle. In myxedema the blood lacks something which the thyroid gland fails to furnish. Sheep's thyroids supply the lack. It is blood poverty, rather than blood infection; but whatever it is, Murray applies his theory, and for a time the patient ceases to be myxedematous. By a reversal of the usual sequence, a pathological condition is made clear by therapeutic means.

There was an appearance of simplicity, also, in the theory of antitoxin, as applied to tetanus and to diphtheria. Behring had isolated an antidote which neutralized the diphtheritic poison. If our theory about it has grown more complex, certainly time has not dimmed the glory of the fact.

Tetanus and diphtheria are local first, and toxic in a general sense afterwards. Their bacilli are known and their poisons can be isolated. When, however, effort was directed toward finding antitoxins for the exanthemata, whose bacilli are as yet unknown, and for tuberculosis, whose toxin refuses to react according to predetermined rules, pathologists encountered difficulties which we, in our ignorant expectation, failed to realize. The past five years have thrown to us much that is obscure and almost discouraging. Editorial contributors have written with easy familiarity about amboceptors and alexins and haptophoric groups. Ideas which are really illuminating have been buried in Greek derivatives and in clumsiness of statement. Little by little, however, theories concerning immunity have precipitated and clarified, so that we can see through a part of them and find suggestions which bewilder, not so much because they are intricate as because they are dazzling with promise of future insight and resource.

In studying the numerous diseases which are manifestly infectious and presumably bacterial, but in which there are, as yet, no recognized bacterial causes, we may be forced to rely upon unproven theory for a long time to come. Smallpox and syphilis are conspicuous examples of this class of diseases. As Lister himself has pointed out, the limit of possible improvement in the power of the microscope may be nearly or even fully reached already. If then, the bacterium of syphilis should chance to be smaller than the bacillus of influenza to the degree in which this bacillus exceeds in smallness the bacillus anthracis, it is improbable that the hypothecated bacterium of syphilis will ever be seen. Moreover, the virus of syphilis, familiar as it is clinically, cannot be made the subject of study by animal experimentation because

¹ Read at the Lister Club, Dec. 18, 1902.

animals other than man possess a natural immunity to syphilis.

And yet we look to pathologists to solve for us problems in artificial immunity, in diseases where it is equally unreasonable to expect either a solution by accident and observation, as was the case with smallpox, or by inductive reasoning and animal experimentation, as was the case with diphtheria.

Light came with the announcement of the so-called "Pfeiffer phenomenon" in 1894. Pfeiffer immunized a guinea pig against cholera in practically the same way that horses are immunized against diphtheria for the production of antitoxic serum, — by repeated injections of cholera cultures. The guinea pig being now immune against cholera, Pfeiffer injected into its peritoneal cavity living cholera vibrios. From time to time by means of glass capillary tubes he withdrew from the peritoneal cavity a small quantity of the exudation, and examined it in the hanging drop. Almost immediately the vibrios lost their motility. In ten minutes they had swollen up and in ten minutes more they had broken into little balls resembling micrococci, which, in another twenty minutes, had been completely lost in the peritoneal exudation. The immune serum had dissolved the bacilli. Pfeiffer had discovered bacteriolysis.

A direct outcome of the Pfeiffer phenomenon was what we know as the Widal test. Gruber of Vienna first observed the agglutination of typhoid bacilli; Widal employed this reaction for diagnostic purposes.

Agglutinins are separate and specific constituents of blood. During the agglutinating reaction, agglutinin is absorbed by the bacteria. This absorption may go on until the agglutinin is entirely used up. It is then possible to dissolve out the agglutinin from the bacteria by dilute alkalies, and after centrifugation, to use the fluid again for agglutinating specific bacteria. According to Buchner, cases have been observed in which the serum has shown distinct power of agglutination, yet no specific protective power.

Still further light was thrown upon agglutinins and bacteriolysins, by the discovery of the hemolytic action, which certain serums exert upon foreign blood. Bordet treated guinea pigs with repeated injections of defibrinated rabbit's blood. This led to the appearance in the serum of the guinea pig of an antibody capable of dissolving rabbit's red blood cells. This antibody is hemolysin, and the process of hemolysis is strikingly analogous to the dissolving of bacteria which constitutes bacteriolysis.

These processes, together with others which are concerned in the various phases of immunity, are outlined in a diagrammatic sort of way by the side chain theory of Ehrlich.

Ehrlich's theory has to do with the production of antibodies. Antibodies are produced only in the living organism. Antitoxin, for instance, cannot be made in a test tube. If we inoculate a dead, sterile, nutrient medium with germs, the number of germs of one kind which we introduce makes little difference. The germs keep on multiplying and eating their food until there is no more food to eat. But in the living body, resistance is more likely to be maintained, and recovery to result, if germs are

introduced in small numbers. It is this resistance which produces an antibody.

Suppose a toxin to be introduced or produced in the organism. When brought in contact with the protoplasm of a cell, the toxin does not become bound to the functioning center of the cell, but to certain side chains or receptors of the cell. The normal function of these receptors is to receive and appropriate food. The molecule of toxin, by its so-called haptophoric group, "catches on" to the side chains of the cell, and after a time (a part of the period of incubation), by the action of its toxophoric group, produces a defect in the cell. These side chains of the cell having been diverted from their function of attracting nutriment, the cell produces new side chains, — sometimes an excess, like the callus of fractured bone. The proliferated side chains have the same affinity for toxin, after they have been cast off by the cell, which they had before; and so, when present in the blood, they constitute an antitoxin.

And now comes an important distinction between the action of a toxin, like that, for instance, of diphtheria, and the action of a bacterium or a foreign blood cell. By direct affinity a molecule of toxin is attracted to the side chains of a cell; but neither a foreign blood corpuscle nor a bacterium can become so attracted, except through the mediation of another body, which acts as a sort of fixer, or mordant, or coupler, by means of which the cell ferment, which is normally present in protoplasm, is able to take part in the production of an antibody.

Ehrlich has shown that in hemolysis the fixer must be anchored to the invading red blood corpuscle. His experiment is as follows: Goat's serum is immunized against sheep's blood, so that the red corpuscles of the sheep are dissolved by the serum of the goat. Then a mixture of the two is heated to 56° C., with the result that no solution takes place. The activity of the cell ferment in the serum of the goat has been checked by heat. Normal, unimmunized goat serum is added, and activity returns: the sheep's corpuscles are again dissolved, because cell ferments are again present. A similar mixture is centrifugalized, and the sediment, consisting of the corpuscles, and the fluid, consisting of the serum, are tested separately. To the fluid, fresh sheep's corpuscles are added, but no reaction occurs; and fresh unimmunized goat serum containing cell ferment is added, but no reaction occurs, because no fixer is present in the fluid. To the sediment, normal serum is added, and complete solution results. The fixers had become anchored to the red cells, and until fixers were present, no reaction could take place.

The fixer in this case must have a twofold affinity, — one for the cell ferment of the host and one for the invading red blood corpuscle. Accordingly Ehrlich calls it an amboceptor. The amboceptor, as already stated, can act only in the presence of the ferment-like body, which is normally present in the protoplasm of the cell, which is easily altered by heat, and which Ehrlich has called the complement.

Besides amboceptor, the following names for the fixer have been used by different writers: preparative, sensitizer, immune body, intermediary body,

desmon. The cell ferment is also known as end body, complement, cytase and alexin.

Most serums contain a variety of cell ferments, which are, as a rule, specific. Normal unimmunized goat's serum can dissolve both guinea pig's blood cells and rabbit's blood cells; but if normal goat's serum is passed through a Pukal's filter, the filtrate can still dissolve guinea pig's blood cells, but its power towards rabbit's blood cells is greatly diminished; that is, the cell ferment in goat's serum which is specifically active towards rabbit's blood is kept back in the filter, while the cell ferment specific towards guinea pig's blood passes through the filter.

The discovery of the presence of specific precipitins in the blood of each species of animal has given us a biological test of recognized medico-legal value — in the hands of experts.

Until recently it has been supposed that snake venom is a poison of the type of diphtheritic toxin, in that it consists of a single body. Venom is normally secreted in the snake by glands analogous to the parotid. The addition of venom to fresh blood of higher animals quickly dissolves the red corpuscles. Sewall Calmette and Fraser, by successive inoculations of snake venom, have produced antivenins which are both protective and curative.

It is now discovered, through the investigations of Flexner and Noguchi, that venom toxin is able to act only through the aid of both fixers and cell ferments. If venom be added to fresh corpuscles which have been washed with isotonic salt solution, so as to remove the cell ferments, the corpuscles are agglutinated but not dissolved. If now a little fresh serum which contains cell ferments is added, the corpuscles are promptly dissolved.

Venom is therefore a body of the type of hemolysins rather than simple toxins. It requires for its activity the presence of fixers which are contained in the venom, and of cell ferments which are normally present in the cells of the victim. Welch's comment upon this discovery, in his Huxley lecture delivered in London last October, is as follows: "That snake-venom should contain only one half of the complete poison, the other and really destructive half being widely distributed in the blood and cells of man and of animals, is an instance of a curious kind of adaptation, of interest from evolutionary as well as from other points of view."

It appears, moreover, that the organism is not only an unexploded potential of self-injury; it is also a mine of self-protection. Wassermann has found that the central nervous system normally contains a substance identical with tetanus antitoxin. He has made an emulsion of fresh tissue from the brain and spinal cord of a guinea pig, and has found that this emulsion is capable of neutralizing the lethal dose of tetanus toxin.

This would seem to show that the presence of antitoxin is not invariably, or at least always discernibly, due to previous introduction of toxin. A condition like this may be one of the forms of natural immunity. Another explanation of natural immunity is absence of side chains having affinity for a given toxin. In such a case, the source of production of a toxin may sometimes be checked by the development of a bacteriolysin.

Explained or unexplained, natural immunity is a

conspicuous fact. A horse, for instance, is two hundred thousand times more susceptible to tetanus than a hen, the amount of tetanus toxin per gram of body weight required to kill a horse being one unit, and to kill a hen 200,000 units. The natural immunity of special tissues finds illustration in the protective agency of skin and mucous membrane. Poisons which are virulent in sub-cutaneous tissue are harmless in the mouth.

No artificial cultivation of special side chains has yet succeeded in producing an immunity so thorough as that which is the result of a previous attack of the special disease itself. Even when immunizing sera shall have become more numerous and more efficient, protests of the anti-vaccinationist type will still be heard, and questions of expediency which are reasonable will also continue to arise. Inoculations against typhoid may be advisable for a soldier about to begin a campaign in South Africa, although inexpedient for the average citizen. The morphine fiend and the arsenic eater of Styria may justly receive a larger measure of disapprobation than is deserved by the faithful boy in his efforts to acquire immunity against tobacco.

Perhaps our ideas of artificial immunity need to be broadened all along the line. Metchnikoff, in his recent book, speaks of a psychical immunity and an immunity which consists in acquired indifference to disagreeable noises, lights and shocks.

Bacteria and red blood corpuscles are not the only foreign cells which have power to develop specialized immune sera. We hear of the employment of immunizing methods for the production of spermotoxins, neurotoxins and nephrotoxins. Within a few months Veit has published results of experiments which seem to show that albuminuria of pregnancy is produced by a lysin called into being by the presence of the placenta.

The injection of Koch's old tuberculin, which disappointed us so sorely as a therapeutic agent, resembles perhaps Act II in the Pfeiffer phenomenon, rather than Act I: the bacilli in the lung produce a half-hearted immunity; injection of tuberculin merely excites reaction.

A reaction, however, is sometimes what we want. Witness, for instance, in certain affections of the joints, the benefit from arterial hyperemia produced locally by hot air. We believe that leucocytes are healers of wounds and absorbers of catgut. Cocci have been thought to aid in checking a slow infection, as when an intercurrent erysipelas has hastened the healing of a tuberculous lung. Even normal salt solution is believed to assist the forces of resistance. Wassermann has recently shown the value of diluting immune serum by the addition of normal serum. Cultures which produced death when combated with immune sera alone were resisted successfully when these same immune sera were fortified by normal serum. Wassermann ascribes this power to excess of normal cell ferments.

The affinities which side chains exhibit are something more than the ordinary positive and negative physico-chemical attractions, such as commonly appear among inorganic bodies. Ehrlich contends that every toxin, every parasitic bacterium and every variety of animal cell has its own specific affinity in side chains of the corporeal protoplasm; or, to state the same thing conversely, that the cells

of the animal body are endowed with separate, specific receptors, having affinities for every kind of invading cell or poison.

If this be granted, it is conceivable that under favoring conditions immunity may be established against anything. One has only to irritate the cell in the proper way, and it will furnish specific side chains for every irritant.

A conception like this is not only striking, it is refreshing. In our therapeutic routine we see so little action we can call specific that it seems good to find in nature such inflexible discrimination.

THE OPEN-AIR TREATMENT OF SYPHILIS.

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I NEVER remember having once seen the open-air treatment of syphilis advocated in any of the many journals of our own country or of other countries; and yet there is, I venture to think, no argument brought forward in favor of the open-air treatment of tuberculosis that is not equally to the point with regard to early syphilis. I suppose that there are a great many, medical men and others, who, because they have not thought about it, have an idea that the open air has some direct influence on the lung tissue in consumptives, just as, I find, there are very many who believe that the cold of these Alpine heights has direct effect on the lung tissue, and on the bacilli in it.

But a little thought will show them that it is not the influence of open air on the lungs which brings about the cure of pulmonary tuberculosis, but that it is the influence of the pure air and sunlight on the blood, and through it on all the other tissues of the body, and chiefly the nervous tissues, that the good results are obtained. Fresh air heightens metabolism in every way, and raises all the tissues to their highest point of resistance, so that they do not succumb to the persistent attacks of the poisons constantly carried hither and thither by the circulating blood.

The nervous system responds the most readily to the purer and richer pabulum brought to its inmost recesses by the blood, and as its cells are better nourished, so its trophic influence is maintained, and the metabolism and growth of all tissues, including the all-important hemopoietic, is ensured and maintained at its highest, and they are thus enabled either actively to beat off, or passively to refuse to succumb to, the specific poisons of any disease.

Open-air life improves the appetite, and again the additional food ingested improves the blood pabulum with the results referred to above. Carefully graduated exercise again increases the appetite and stimulates the emunctories, and helps the elimination of their excreta. Rest, much rest, carefully prescribed at suitable times and under correct conditions, again helps much. And if this can all be done away from home surroundings and worries, in a high, dry, bracing climate, with the purest possible air, with pleasant companions and environment, the greater will be the efficacy and permanency of the whole treatment.

Open air, then, rest, high feeding, graduated exercise and if possible a bright, dry, bracing climate, are our means for enabling an individual to escape the eventual horrors of consumption. But all and each of these are, in my opinion, as important in enabling the individual to escape the eventual horrors of syphilis (with the help of small doses of mercury maintained for many years).

The parallel is strict. The poison, — whether it be a bacillus or a ferment, an enzyme, a toxic-albumose, or we know not what, is there, — in the individual. It is somewhere in the system. It may be weak; it may be strong. Or the resisting power of the individual's tissues may be weak; or may be strong. Or the idiosyncrasy of the individual may be such as to render him well-nigh immune or particularly susceptible. The poison may be causing actual physical signs and symptoms, or it may be apparently latent, but powerful for evil, and perhaps gaining strength wherewith to strike with thuglike precision and force when long forgotten and least expected, and when inadvertently the unwary victim has laid himself open to attack by being run down through worry, overwork, or neglected ill-health.

It matters not whether the poison be the syphilitic or tubercular, — it may suddenly seize upon the lungs, larynx, nervous system or connective tissues. Surely if the open-air treatment is called for at the beginning for the one, it is equally so for the other, to avert the staggering consequences of the original infection. And yet I have never seen it advocated equally for both.

In syphilis, mercury undoubtedly does good. Probably until the last thirty years it has, I think, done more harm than good. It is not an antidote to the syphilitic poison any more than iodide of potassium is. It probably helps the tissues of the syphilitic, much as I find that arsenic sometimes seems to help the tissues of the tuberculous. I do not feel that it is a "specific," and Diday, whose work on the subject seems to me to carry much weight and conviction, certainly seems to teach the same.

During ten years in a busy practice in the university town of Cambridge, I saw many young men with early syphilis, and I often kept in touch with them for many years after they had gone down from the university. And one thing impressed me much; that whereas a poor, under-fed scholar, if infected, was hit painfully hard, the well-to-do hunting or athletic undergraduate generally suffered lightly. The latter led an open-air life, he ate meat three times a day, his tissues were well nourished, and therefore at a high resistance pitch. But the scholar, often poor, trying, because of the *res angustæ domi*, to live on his scholarship, who generally had porridge for breakfast, bread and jam for lunch, and a poor dinner in the hall, sometimes at a dreadful time of day, badly served and hastily eaten or left, he, I noticed, often suffered badly. And this, too, in spite of the fact that the sporting undergraduate was often very casual about taking his mercury. He very often, however, got off cheap, had but slight secondaries, and heard no more of his trouble. For, later on, he continued to live a well-fed, open-air life, often as a country gentleman, or in some other easy-going position in life.